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Mathis, C., and C. H. Malbert. Erythromycin gastrokinetic activity is partially vagally mediated. *Am. J. Physiol.* 274 (*Gastrointest. Liver Physiol.* 37): G80–G86, 1998.—Erythromycin overcomes postvagotomy gastroparesia in patients without a distal stomach and functional pylorus. We investigate the role of the vagus in gastric emptying increased by erythromycin, using a model that preserves the physiology of the distal stomach and pylorus. The effects of erythromycin lactobionate (10 mg/kg) on transpyloric flow pattern and pyloric resistance were evaluated during repetitive bilateral vagal cooling in anesthetized pigs. Vagal cooling during erythromycin infusion produced a marked decreased of pyloric outflow (23 ± 1.1 vs. 50 ± 2.6 ml/min) related to a reduced stroke volume of the flow pulses (7.8 ± 3.31 vs. 14.1 ± 2.44 ml). The amplitude and frequency of gastric and duodenal pressure events were unchanged or slightly reduced during vagal cooling. The smaller stroke volume of flow pulse was the consequence of increased pyloric resistance (6.2 ± 1.98 vs. 2.3 ± 0.21 mmHg·ml^{-1}·s), which is associated with changes in the temporal relationship between a pyloric pressure event and flow pulse. In conclusion, erythromycin activity on the pylorus requires the integrity of vagal pathways. Enhancement of gastric outflow by erythromycin is also modulated by the vagus, since pyloric resistance was able to overcome increased gastric motility.

motilin; vagus; pyloric resistance; erythrolides; gastric emptying

ERYTHROMYCIN is one of the most potent prokinetic agents in humans and animals (30). It is believed that the vagus is not involved in the increased gastric emptying rate induced by erythromycin, but experimental evidence is limited and biased. Indeed, improved gastric emptying reported in the literature described vagotomized patients with functional (pyloroplasty) or anatomic (Roux Y or antrectomy) removal of the distal stomach, including the pylorus (6a, 15, 27, 32). These models are consistent with the clinical situation, since truncal or selective vagotomies are always associated with drainage, i.e., pyloroplasty or/and antropylorectomy. However, it is impossible to ascertain that the activity of erythromycin in intact subjects does not involve the vagus, and it cannot be excluded that erythromycin acts, especially on the pylorus, through vagal pathways. This has already been suggested by Inatomi et al. (17), who found that low doses of an erythromycin-like compound, EM-574, were ineffective at increasing gastroduodenal motility during vagal cooling.

Regional differences are involved in erythromycin prokinetic activity: erythromycin has an excitatory influence in the stomach and an inhibitory one in the pylorus. Erythromycin excitatory activity relates to contractions of greater amplitude and frequency on the stomach and small intestine (11, 16, 28) and increased proximal gastric tone (5). Alternatively, erythromycin also increases gastric emptying caused by reduced pyloric resistance, since in humans erythromycin decreases the number of isolated pyloric pressure waves (IPPWs) and pyloric tone (11). Both pyloric patterns are atropine sensitive (10) and partially controlled by vagal pathways (24).

The aim of this study was to investigate the role of the vagus in erythromycin activity with special reference to the pylorus. Vagal continuity was altered by acute cooling of the nerve trunks during measurements of transpyloric flow and pyloric resistance.

MATERIALS AND METHODS

Experimental design. Ten Large White female pigs (mean weight 35 ± 3.6 kg; age 4 mo) were used. The animals were fasted for 24 h before each experiment. Recordings were made with the animals in a dorsal recumbent position. Recordings started at a minimum of 160 min after completion of the surgical procedure. This delay was necessary to observe at least one regular activity phase of the migrating motor complex. At completion of this phase, saline was infused into the stomach (12 ml/min), and data recorded indicated that the duodenal outflow rate was permanently equal to or higher than 10 ml/min (23, 24). The control corresponds to a period lasting 90 min, which started once the transpyloric flow was stabilized according to the former criteria.

Erythromycin lactobionate (Abbott; 10 mg/kg) was administered intravenously as an infusion, diluted into 50 ml of 0.9% saline over a period of 40 min. Infusion was accomplished through a catheter surgically located in the right jugular vein. Infusion of erythromycin was performed once in each animal, since repetitive infusions did not produce identical motor effects (33).

To evaluate the role of the vagus on erythromycin-induced changes in pyloric resistance and transpyloric flow patterns, reversible cervical bivagotomies were performed, using two cooling jackets (2, 12) placed around the left and right vagi. Cooling procedures lasted 3 min, during which the temperature of the vagus was maintained at 1 ± 1°C, and were performed at 10, 20, and 30 min after the start of erythromycin infusion. The efficacy of vagal cooling to suppress vagal traffic was confirmed by a >20% increase in heart rate.

Anesthesia. Pigs were preanesthetized with ketamine (5 mg/kg im; gift of Rhone Merieux). Suppression of the pharyngotracheal reflex was obtained by administering halothane (5% vol/vol) through a face mask immediately before intubation. A venous cannula was inserted into the marginal vein of the ear to infuse a mixture of α-chloralose (60 mg/kg; Sigma) and urethan (500 mg/kg; Sigma), which was used alone for the remainder of the study. The pigs were mechanically ventilated by a Siemens SAL 9000 ventilator with a tidal volume of 15 ml/kg at a respiratory rate of 18 breaths/min. Ventilation was adjusted to obtain normocapnia (end-tidal

CO_2 pressure at 35–45 mmHg). Normocapnia was measured with the use of an infrared capnograph (Engström Eliza) with air sampling at the Y piece of the ventilator. Fractional inspired oxygen was adjusted between 20% and 100% using pulse oxymetry (partial oxygen pressure) data supplied by a sensor (Ohmeda, pulse oxymeter) attached to the tail. A catheter inserted in the carotid artery was used to measure heart rate and systolic, diastolic, and differential pressures. A surgical level of anesthesia was maintained by supplemental injection of chloralose-urethan mixture, performed when the heart rate increased by >20% or when systolic and differential pressures increased by >20%. Supplemental administration of anesthesia was not performed during erythromycin infusion. Rectal temperature was maintained constant (38.5 ± 0.5°C) with the use of a heating pad.

Animal preparation. A midline abdominal incision was performed to insert sensors designed to measure motor activity and transpyloric flow. A manometric assembly incorporating three side holes (antrum −5 and −2 cm, pylorus and duodenum +0.5 cm) and a sleeve sensor (4 cm length) was located astride the pylorus (23, 24). A flowmeter probe was inserted in the duodenal lumen (25). The duodenal effluent was drained through a tube (8 mm ID) with its tip positioned 12 cm from the distal end of the flowmeter. A larger tube (10 mm OD, 8 mm ID) was inserted 15 cm orad to the pylorus to infuse saline in the stomach. The vagal trunks were prepared using microdissecting techniques *1*) to remove the connective tissue and *2*) to separate the vagal bundles from the sympathetic trunks that were not blocked during cooling (Fig. 1).

Measurements. Manometry side holes were perfused with degassed water, using a low-compliance pneumohydraulic pump (IP 8000, Gould) at 0.3 ml/min. The sleeve channel was perfused at 0.5 ml/min. Sudden occlusion of each side hole resulted in an increase in pressure over 400 mmHg/s. Pressures were digitized on line at a frequency of 10 Hz using a microcomputer (Macintosh II, Apple Computer) with an analog-to-digital card (NB MIO 16, National Instruments, Austin, TX; MAD, Synectics, Stockholm, Germany; and LabView 3.1, National Instruments). Data were stored continuously on a hard disk for further analysis.

The flow probe was connected to an electromagnetic flowmeter as previously described (23). Retrograde flow was detected as a deflection of the flow path below the baseline. Duodenal effluent was continuously weighed by a load cell (QB 742, Phi Mesure) for subsequent determination of nonpulsatile flow. Flow rate and duodenal effluent volume were also recorded on the hard drive.

Data analysis. Analyses were performed automatically, using MAD (1, 24). Pressure changes <10 mmHg were not considered to be pressure waves. Isolated pressure waves (IPPWs) were defined as pressure events occurring at the sleeve channel without terminal antral or duodenal pressure events (14). The flowmeter probe allowed the recognition of pulsatile transpyloric flow, and flow pulse characteristics were detected according to published algorithms (24). Nonpulsatile flow was quantified by subtracting the volume of pulsatile flow from the total volume of the duodenal effluent. Pyloric resistance was computed from pressure and flow data using the relationship between the pressure gradient astride the pylorus and flow rate.

Statistical analysis. One-way analysis of variance (ANOVA; $P < 0.05$ indicated significance) was used for statistical analysis. Data are expressed as means ± SD.

RESULTS

Transpyloric flow. Gastric emptying increased (50 ± 2.6 vs. 11 ± 4.5 ml/min, $P < 0.05$) ~5 min after the start of erythromycin intravenous infusion. Gastric emptying was exclusively pulsatile and backflow was absent, whereas during control backflow amounted to 9% of the forward flow. Flow pulse stroke volume was doubled compared with control because peak flow and duration of the flow pulses were significantly increased (Table 1). Flow pulse frequency was unchanged during erythromycin infusion.

About 15 s after vagal temperature reached 1°C, the volume emptied was significantly reduced compared with erythromycin alone (23 ± 1.1 ml/min). Gastric

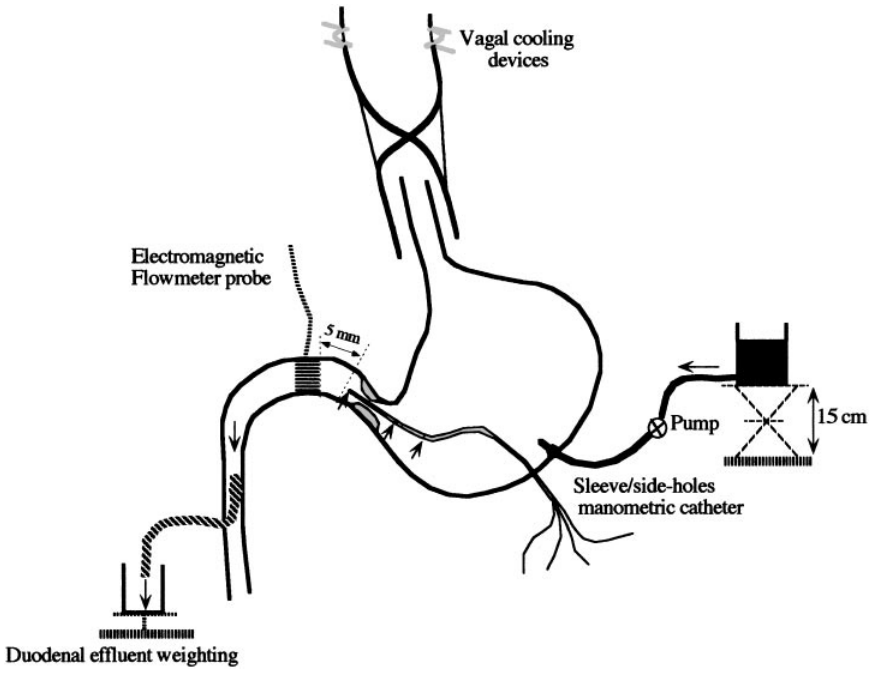

Fig. 1. Surgical preparation. Arrows indicate location of side holes along the catheter assembly. Duodenal outflow values are reset automatically to zero when 80 ml of duodenal juice are present in the collecting reservoir. Stainless steel tubing, forming a hook incorporating a temperature sensor, was located around the cervical vagal trunks and used as a vagal cooling device.

Table 1. *Characteristics of individual transpyloric flow pulses during infusion of erythromycin lactobionate (10 mg/kg iv) with or without bilateral cervical vagal cooling*

	Control	Erythromycin	Erythromycin/ Vagal Cooling
Stroke volume, ml	3.5 ± 0.43	14.1 ± 2.44*	7.8 ± 3.31†‡
Pulse duration, s	7.0 ± 0.26	10.8 ± 0.49*	8.1 ± 0.77†
Peak flow, ml/s	1.7 ± 0.41	4.4 ± 0.92*	2.8 ± 0.71†‡
Frequency, min^{-1}	3.3 ± 0.51	4.0 ± 0.44	3.2 ± 0.77

Values are means ± SD for n = 10 pigs. *Erythromycin significantly different from control. †Erythromycin during vagal cooling significantly different from erythromycin without vagal cooling. ‡Erythromycin during vagal cooling significantly different from control.

emptying remained pulsatile, but the characteristics of the flow pulses changed (Fig. 2). Stroke volume was halvedbecause of a shorter duration and reduced peak flow (see Table 1; $P < 0.05$). Flow pulse frequency was not modified by vagal cooling. Gastric emptying resumed, and the characteristics of flow pulse were not significantly different from erythromycin alone ~50 s after the end of vagal cooling.

Motor activity. Basal pyloric pressure decreased significantly during erythromycin infusion, from 18.2 ± 0.69 to 5.2 ± 3.07 mmHg ($P < 0.05$), resulting in a sixfold increase of the antroduodenal pressure gradient (6.1 ± 0.61 mmHg, $P < 0.05$, Fig. 3). Erythromycin induced pressure events on the formerly quiescent antral −5 cm side hole and increased by ~60% the amplitude and frequency of the pressure events at −2 cm (Table 2). Amplitudes and frequencies of pyloric and

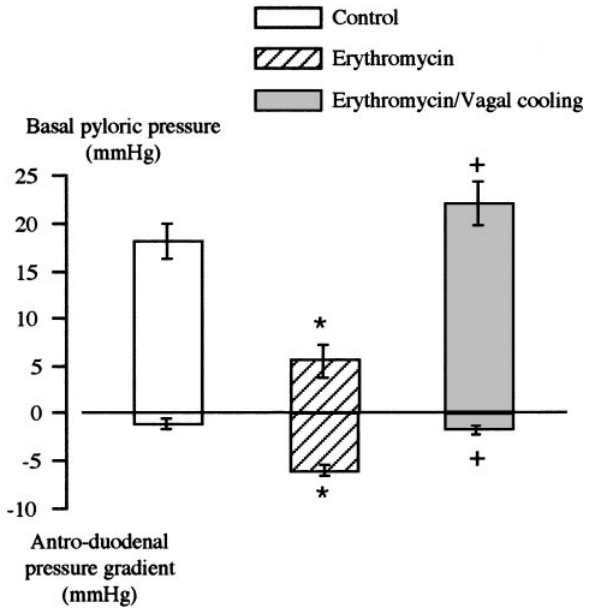

Fig. 3. Basal pyloric pressure and antroduodenal pressure gradient during erythromycin infusion with and without vagal cooling. Basal pyloric pressure was reduced and antroduodenal pressure gradient doubled by erythromycin. These effects were abolished by vagal cooling. *$P < 0.05$ vs. control. $^{+}P < 0.05$ vs. erythromycin.

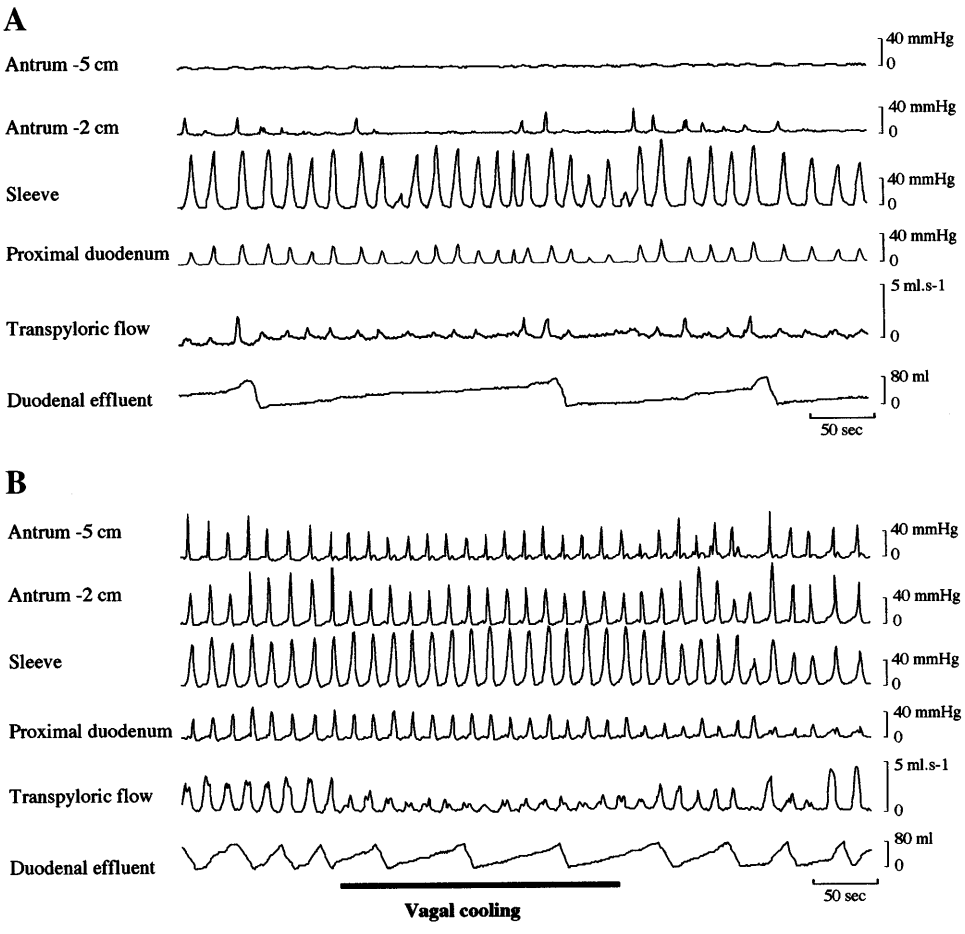

Fig. 2. Changes in antroduodenal motility and transpyloric flow induced by intravenous infusion of erythromycin lactobionate without and with vagal cooling. Erythromycin (*B*) induces well-defined flow pulses with increased stroke volume compared with saline (*A*; control). During vagal cooling, peak flow was drastically reduced without major changes in gastric or duodenal motor patterns.

Table 2. *Characteristics of pressure events during infusion of erythromycin lactobionate (10 mg/kg iv) with or without bilateral cervical vagal cooling*

	Control	Erythromycin	Erythromycin/ Vagal Cooling
Amplitude, mmHg			
Antrum −5		37 ± 8.0	35 ± 6.2‡
Antrum −2	21 ± 3.1	54 ± 5.6*	37 ± 4.6†
Sleeve	40 ± 3.5	55 ± 4.9*	56 ± 8.6‡
Duodenum	20 ± 2.3	31 ± 4.0*	17 ± 3.4†
Frequency, min^{-1}			
Antrum −5		4.0 ± 0.53	1.6 ± 0.19†‡
Antrum −2	1.4 ± 0.23	4.0 ± 0.31*	4.0 ± 0.22‡
Sleeve	3.3 ± 0.15	4.4 ± 0.09*	3.7 ± 0.27
Duodenum	3.0 ± 0.23	4.0 ± 0.26*	3.9 ± 0.22‡

Values are means ± SD for $n = 10$ pigs. Pressure events were recorded 5 and 2 cm proximal to the orad end of the sleeve (Antrum), at the pylorus (Sleeve), and 0.4 cm distal to the end of the sleeve (Duodenum). *Erythromycin significantly different from control. †Erythromycin during vagal cooling significantly different from erythromycin without vagal cooling. ‡Erythromycin during vagal cooling significantly different from control.

duodenal pressure events increased by 30%. IPPWs were absent during erythromycin infusion. The time interval between antropyloroduodenal pressure events occurring in series was significantly shortened by erythromycin, with pressure events occurring within a 1-s time period.

Vagal cooling significantly increased basal pyloric pressure (22.1 ± 1.84 mmHg) and reduced the antroduodenal pressure gradient (2.0 ± 0.32 mmHg, $P < 0.05$). The frequencies of antral, pyloric, and duodenal pressure events were unchanged compared with erythromycin alone. The amplitudes of pressure events at −2 cm and at the proximal duodenum were significantly reduced, whereas they were identical at −5 cm and at the pylorus. IPPWs were not recorded during vagal cooling. Vagal cooling resulted in a significant increase of the time interval between antropyloroduodenal pressure events (>1 s).

Pressure-flow relationships. The interval between pyloric pressure events and flow pulses was significantly reduced during erythromycin infusion. During erythromycin infusion, flow pulses occurred 1.0 ± 0.31 s before pyloric pressure events, compared with 3.2 ± 0.58 s before pyloric pressure events for control (Fig. 4). Erythromycin halved pyloric resistance (2.3 ± 0.21 vs. 4.6 ± 0.46 mmHg·ml^{-1}·s, $P < 0.05$).

During vagal cooling, the interval between pyloric pressure events and flow pulses was significantly increased (1.9 ± 0.33 s). Pyloric resistance was three times greater than during erythromycin alone (6.27 ± 1.98 mmHg·ml^{-1}·s). Resistance recovered its former value ~50 s after completion of the cooling period (Fig. 5).

DISCUSSION

We have shown the existence of a vagal pathway that participates in erythromycin prokinetic effects. This pathway primarily modulates the motility and resistance of the pylorus.

The most important result of our study was that the increased gastric emptying rate induced by erythromycin was suppressed by vagal cooling. This demonstrates that vagal pathways are essential for gastrokinetic activity induced by erythromycin. This result does not intrinsically contradict former studies in humans and dogs (6a, 15, 27, 32), although we reached a different conclusion. In previous studies, we also found that vagal section does not drastically modify erythromycin-induced increases in antral and duodenal motility. A decreased emptying rate was not observable in vagotomized patients with drainage because in these patients

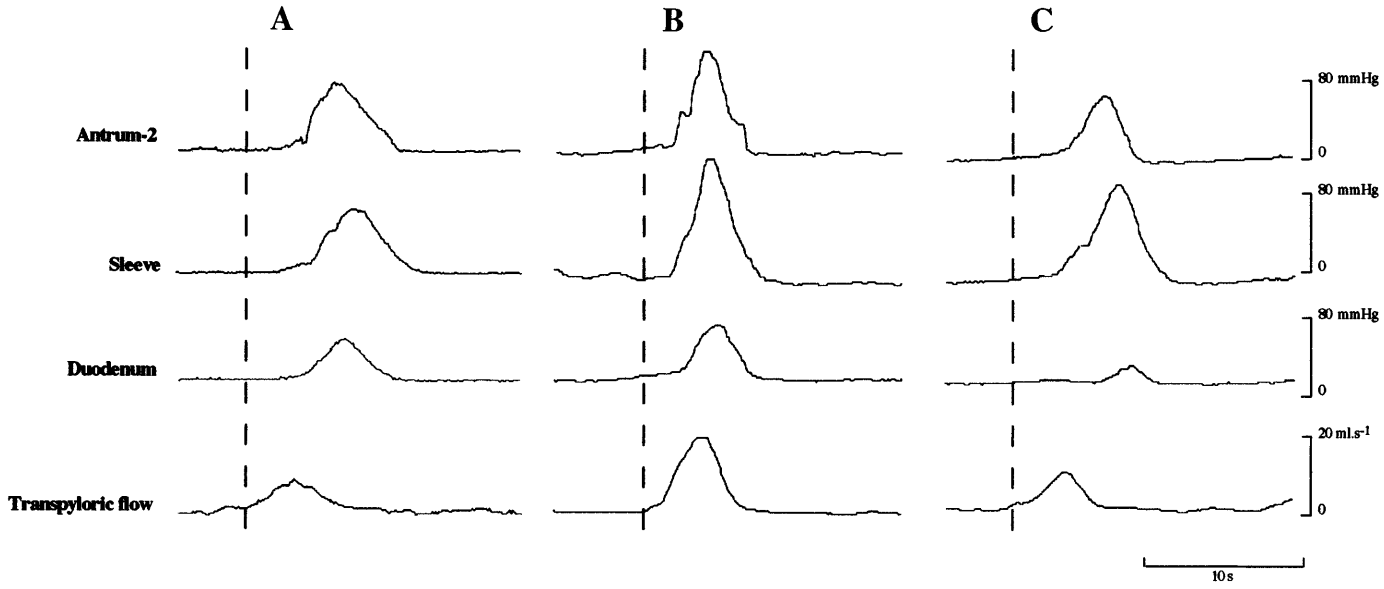

Fig. 4. Time intervals between antropyloroduodenal pressure events and transpyloric flow pulses during erythromycin infusion with (*C*) and without (*B*) vagal cooling. *A*: control. The shorter time interval between pyloric pressure event and the flow pulse induced by erythromycin alone was abolished during vagal cooling. Dotted line represents onset of flow pulse.

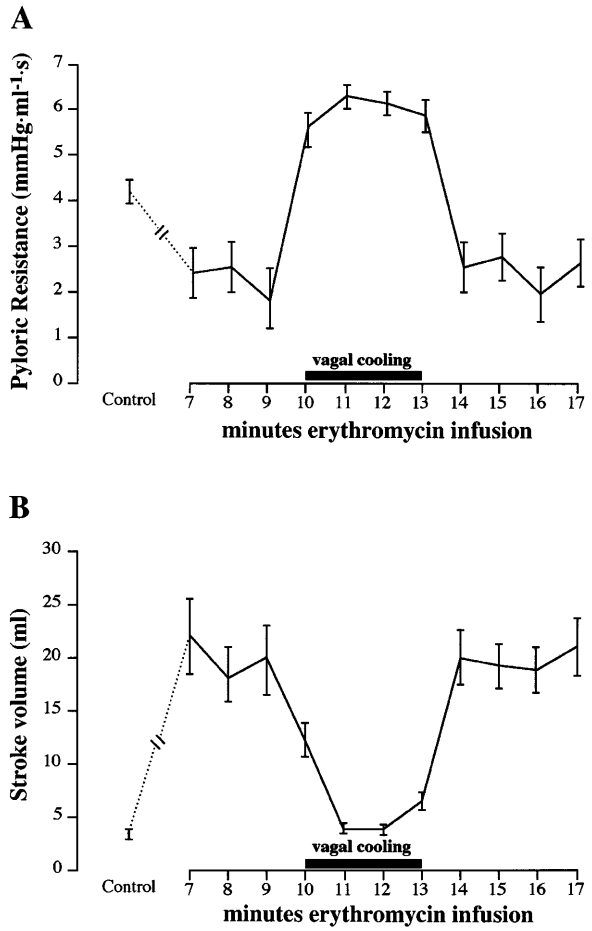

Fig. 5. Pyloric resistance (*A*) and flow pulse stroke volume (*B*) during erythromycin infusion with and without vagal cooling. Vagal cooling increased pyloric resistance that had been reduced by erythromycin, indicating the existence of a vagal pathway in erythromycin activity. Abscissa represents minutes after the start of erythromycin infusion. Data are mean values over a 1-min period. Black bar shows vagal cooling at 1°C; periods during which temperature was between 2°C and 38.5°C were not included.

the pyloric area has been removed or made not functional.

Our results must be interpreted with the knowledge that the regulatory mechanisms may be altered by the experimental conditions. Despite use of state of the art monitoring and anesthesia methods it cannot be ruled out that anesthesia might interfere with gastropyloroduodenal motility. Nevertheless, the physiological relevance of our animal preparation is clearly demonstrated by the effects of erythromycin on gastropyloroduodenal motility that are strictly identical to those observed in conscious humans, using a similar manometry recording setup (11). In humans (11) and in our pig preparation, erythromycin decreased pyloric tone, suppressed IPPW, and increased frequency and amplitude of distal antral and duodenal pressure waves. In both preparations, there was also an activation of proximal antral motility that was formerly quiescent. Furthermore, from a quantitative point of view, the mean amplitude increase of pressure waves recorded at the distal antral site was 50 mmHg or more after erythromycin in humans and in our pig preparation. Hence it is virtually impossible either quantitatively or qualitatively to distinguish the motor effects produced by erythromycin in consious humans vs. anesthetized pigs. Because the motor effects of erythromycin were not modified in our anesthetized pig preparation, it is likely that neither the effects on transpyloric flow nor the changes induced by vagal cooling are altered compared with conscious animals.

The results presented in this study are not likely to be associated with vagal denervation hypersensitivity (7). First, different effects of vagal cooling were observed on the antroduodenum and on the pylorus, respectively. Second, we have demonstrated in an identical anesthetized pig preparation that vagal tone toward pyloric motility and resistance was limited (24). Finally, we have shown that vagal stimulation is always associated with decreased pyloric resistance (24), whereas in this study pyloric resistance increased during vagal cooling plus erythromycin administration.

During vagal cooling, while erythromycin was infused, we observed a decreased transpyloric flow together with *1*) an increased pyloric resistance and *2*) an increased antroduodenal motility. This motor profile and its functional outcome are identical to that demonstrated in dogs immediately after the administration of cisapride (26). Although it is highly unlikely that the same nervous mechanisms were involved, the mechanical significance is similar. Increased pyloric resistance is able to overcome a paramount increase in propulsive forces generated at the gastric level.

The reduced erythromycin-induced gastric emptying observed during vagal cooling might have multiple origins. Despite a clear effect of vagal cooling on pyloric resistance, a possible involvement of proximal gastric tone cannot be ruled out. Indeed, erythromycin enhances fasting and postprandial proximal gastric tone in humans (5), and gastric tone is known to be primarily regulated by vagal inputs (3). Therefore it is possible that propulsive forces generated by erythromycin might be decreased during vagal cooling through a decreased proximal gastric tone. In contrast, the influence of increased duodenal resistance and/or decreased duodenal compliance (25) induced by vagal cooling is unlikely, since their quantitative importance for gastric emptying is reduced by insertion of a Foley catheter in the duodenum.

The reduced emptying rate is related to an increased pyloric resistance and not to a decreased antral motility, indicating that erythromycin acts on pyloric resistance and on gastric phasic motility through different pathways. These interactions with vagal pathways were similar those described for motilin (8, 34). Debas et al. (9) found that motilin, as did erythromycin in this study, increases gastric emptying of liquids in dogs only if the vagal innervation is intact. Furthermore, the aforementioned interactions are in accordance with the suppression of gastric emptying effects of erythromycin after ganglionic blockade by hexamethonium (16). Inatomi et al. (17) suggested that erythromycin, like EM-574 and motilin, might stimulate vagal cholinergic

neurons. On the contrary, the persistence of the effects of erythromycin on gastric phasic motility during vagal cooling might involve a local action of erythromycin (13, 29), probably via activation of motilin receptors or nonvagal cholinergic neurons in the enteric nervous system (17).

The sites of interaction between erythromycin and vagal neurons cannot be determined from our experimental data. A direct action of erythromycin on motilin receptors located either directly on the vagus or centrally cannot be excluded, since motilin immunoreactivity has been found at these locations (4, 35). An alternative, not exclusive to the direct action of erythromycin, is that the central action of erythromycin is not related to erythromycin itself but to another factor. It has been suggested that the final nervous pathway for erythromycin derivative (EM-523) might involve facilitation of serotoninergic transmission (18, 31). A similar regulation has also been demonstrated for motilin (20). As for motilin receptors, 5-hydroxytryptamine$_3$ receptors have been found in the area postrema (21, 22) and on the vagus nerves (6, 19).

Although erythromycin is still active in the stomach and the duodenum after vagotomy, the increased emptying rate induced by erythromycin was not observed in vagotomized animals. An increased pyloric resistance together with decreased emptying rate obtained during vagal cooling indicate that erythromycin effects in vivo are partially mediated by the vagus.

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